DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 5, 2010 has been entered.

Claim Amendments

2. The amendment filed February 5, 2010 have been entered. Claims 1-2, 9 and 23 have been entered. Claims 39-40 have been newly added. Claims 11-12, 18-22 and 28-36 are cancelled. Claims 1-10, 13-17, 23-27 and 37-40 are under consideration in this Office Action.

Withdrawal Of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments:

a) The rejection of claims 1-5, 8, 10, 14-17, 23-27 and 37-38 under 35 U.S.C. 103(a) as being unpatentable over Doshi et al., and Aunet et al., in view of Zierdt et al;

b) The rejection of claims 6 and 7 under 35 U.S.C. 103(a) as being unpatentable Doshi et al., and Zierdt et al., further in view of Cathey et al; and

c) The rejection of claims 9 and 13 under 35 U.S.C. 103(a) as being unpatentable over Doshi et al., Aunet et al., and Zierdt et al., further in view of Besson-Faure et al.

Response to Arguments

4. Applicant's arguments with respect to claims 1-10, 13-17, 23-27 and 37-40 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection Necessitated By Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-5, 8, 10, 14-17, 23-27 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doshi et al., (US Patent 5,766,552 published June 16, 1998) and Zierdt (US Patent 4,435,505 published March 6, 1984) in view of Zierdt et al., (J. of Clinical Microbio. 1982. Vol. 15(1):74-77).

The claims are drawn to a method for detecting contaminating microbes possibly present in a blood product comprising blood cells comprising: a) providing a sterile device for concentrating microbes possibly present in a blood product containing blood

cells comprising a first watertight, sterile tank containing a piston and at least one blood cell aggregation agent and, optionally, at least one marker agent for labeling pathogenic microbes: a second watertight, sterile tank containing at least one lysis agent for blood cells and, optionally, at least one marker agent for labeling pathogenic microbes; a first filter located between the first tank and the second tank and having pores: a second filter enclosed in a membrane support having two removable, separable parts and located downstream of the second tank and having pores;

a first watertight, sterile connector joining the first tank and the first filter;

a second watertight, sterile connector joining the lust filter and the second tank;

a third watertight, sterile connector joining the second tank and the second filter;

a fourth watertight, sterile connector comprising a reverse lock valve and joining a bag containing a blood product to the first sterile tank,

b) subjecting a sample of the blood product to an aggregation treatment of the blood cells in the first tank, c) substantially eliminating aggregates formed in step (b) by passage of the sample over the first filter to allow passage of contaminating microbes, but not cell aggregates, d) selectively lysing residual cells of the filtrate obtained in step (c) in the second tank, e) labeling the contaminating microbes with a marker agent either during step (b) or step (d), f) recovering the contaminating microbes by passage of the lysate from step (d) over a second filter to retain contaminating microbes and allow passage of cellular debris, and g) analyzing material on the second filter to detect labeled contaminating microbes possibly retained by the second filter, said method being performed in the sterile device.

Doshi et al., teach that the separation of serum or plasma from whole blood is extremely important since it is difficult to conduct the analysis of dissolved blood components without interference from red blood cells (col. 1, lines 47-50). Red blood cells (RBC) are removed from whole blood samples by contacting a whole blood sample with an agglutinating agent (col. 7, lines 25-28). The agglutinating agents allow for the quick and efficient formation of clusters of RBC, be fast acting, have short reactivation time, are non-specific to blood types, and be stable and inexpensive (col. 5, lines 32-34). Doshi et al., teach antibodies as agglutinating agents since they are reactive and well known for agglutinating erythrocytes (col. 7-8, lines 66-6). These antibodies should recognize antigenic surface constituents such as glycoproteins (col. 8, lines 6-10).By contacting the RBC with agglutinating agent, the cells are agglutinated and trapped by the pad while the remainder of the fluid sample flows through readily (col. 6, lines 10-15). Doshi et al., teach the efficiency of filtration, along with the lysis of RBC wherein whole blood is passed through the filter and plasma is retained (col. 8, lines 54-56). Doshi et al., teach the removal of the RBC clusters by filtration (col. 11, lines 40-41). The preferred filtration uses a porous absorbent pad with mesh or pore size being from about 20 to about 500 microns (col. 62-65). This is within the instantly claimed size of pores for the first filter. The secondary filter is used to trap red blood cells and has a very small pore size to permit plasma to pass (col. 12, lines 1-11). Doshi et al., teach having a reactant pad through which the fluid flows to allow for the production of a detectable signal (col. 14, lines 39-41). The analyte reacts with the reagents to produce a detectable signal such as dyes, particles, and proteins with visible extinction

coefficients (col. 14, lines 42-43). Thus, where the analyte is an enzyme substrate, the pad may be impregnated with the appropriate enzyme or enzymes to produce a product that is measured (col. 15, lines 10-13). The production of a detectable signal produced by enzymes teach the marker agent. The method teaches a measurement dye zone wherein the zone is coated or impregnated with an indicator material that reacts with the enzyme treated sample to give an indication of the presence or amount of analyte in the sample (col. 16, lines 23-27). Thus the indicator material that reacts with the enzyme treated sample material is the marker agent.

Doshi et al., teach one type of RBC agglutinating agent is lectins, including *Phaseolous vulgaris* (col. 7, lines 46-48). Other agglutinating agents include antibodies that have a binding affinity for a determinant present on the surface of red blood cells that recognizes antigenic surface constituents (col. 7-8, lines 65-8). Doshi et al, teach a minimum amount of antibody must be used in the blood separation device (col. 8, lines 43-45). Doshi et al., state that one skilled in the art will readily determine the optimum amount of antibody to be used in the method (col. 8, lines 49-51). Thus Doshi et al., teach using an appropriate concentration of antibody. The use of detergents where a lipophilic analyte is in the blood is disclosed (col. 15, lines 27-28). The detergents are anionic or cationic detergents (col. 15, lines 33). Thus the art teaches using cationic and anionic detergents. Doshi et al., teach using various sticking agents or adhesives (col. 15, lines 38-41). These sticking agents would meet the permeabilization agents. However, Doshi et al., do not teach the method being performed in a sterile device as instantly claimed which further comprises selectively lysing the cells and recovering

microbes with second filter which retains contaminating microbes and allows passage of cellular debris.

Zierdt (US Patent 4,435,505) teaches an apparatus for blood sample treatment involving lysis, filtration in a simple and efficient manner with minimum risk of contamination (col. 2, lines 15-20). The apparatus has three filters, two chambers, conduit tubing throughout, valves, clamps and a lysing chamber (Figure 1). Zierdt teaches the system provides superior performance in that the phagocytes of the blood are killed and lysed, releasing bacteria that would otherwise be killed by phagocytic action (col. 1, lines 54-57). Other possible advantages are the removal from the blood culture of antibiotics, if present in the patient's blood (col. 1, lines 57-59). Also removed via the filtrate are antibodies, complement, and opsonins. In other words, the removal is accomplished of all the anti-bacterial mechanisms of whole blood. Zierdt teaches remaining on the filter membrane, which is then cultured, are red blood cell membranes, white blood cell membranes and nuclei, platelets, and such microorganisms which happen to be present (col. 1, lines 64-67). Although the system will trap mycoplasma and chlamydia, the bulk of microorganisms cultured are bacteria and fungi (col. 1-2, lines 1-68-2). Zierdt teaches an apparatus (11) comprises an upper chamber (12) which may be substantially cylindrical in shape and has a top wall with an upwardly directed inlet conduit (14) normally covered by a removable cap 15 (col. 3, lines 1-6). The cap 15 is provided internally with a porous filter material (17) as shown in FIG. 1 (col. 3, lines 6-8). The cap can act as a valve which joins the bag of blood or the injectable source containing the blood to the tank. Cap 15 is readily removable to allow

injection of a blood sample to be processed (col. 3, lines 9-10). Therefore the ability to inject blood allows for the sterile tank to contain a piston. Zierdt teaches an upper chamber (12) with a spout (19) (col. 3, lines 11-12). The portion of the cylindrical wall of upper chamber (12) extending below the bottom wall as shown in FIGS. 1 and 2. Zierdt teaches inlet conduits (22) and (23). Conduit (22) is connected to a flexible plastic conduit (24) leading to a flexible bag (25) containing lysing solution, such as Triton X-100, $NaHCO_3$-Na_2CO_3 buffer also known as sodium carbonate (col. 3, lines 21-25). The conduit (24) is normally closed off by a conventional clamp (26) located adjacent to the chamber inlet conduit (22) (col. 3, lines 25-27). Zierdt teaches filter membrane (30) of suitable porosity, for example, about 0.6 μM pore membrane (col. 3, lines 36-37). The lower chamber (33) has a side conduit (39) connected to a conduit (40) which includes filter material and can be at times connected to a suitable vacuum source (col. 3, lines 50-54). Zierdt teaches the entire apparatus is normally enclosed and suitably sterilized (col. 3, lines 55-57).

Zierdt et al., (J. of Clinical Microbio.) teach selectively lysing the cells and recovering microbes with second filter having a pore size of about 0.3um to less than 1um which retains contaminating microbes and allows passage of cellular debris (page 74 col. 2 and page 75, col.1). Zierdt et al., teach running the lysed blood samples through a filter sized at 0.45um which thereby has a pore size of about 0.3um to less than 1um and can retain contaminating microbes yet allow passage of cellular debris (page 75, col.1). Zierdt et al., teach the superiority of the lysis-filtration procedures (page 75, col. 2). Zierdt et al., teach increased sensitivity in the detection of bacteremia

(page 77, col. 1). Zierdt et al., teach techniques were blood sample was treated with a lysing solution to release intracellular bacteria and then membrane filtered which had the advantage of separating bacterial pathogens from all antibacterial properties of the blood including antibodies, complement, phagocytes and antibiotics (page 74, col.1).

Therefore, it would have been *prima facie* obvious at the time of applicants' invention to modify the method of Doshi et al., to include an enclosed and sterile device of Zierdt (US Patent 4,435,505) and the lysing step and second filter that retains contaminating microbes and allows passage of cellular debris as taught by Zierdt (US Patent 4,435,505) and Zierdt et al., (J. of Clinical Microbio.) because Zierdt et al., teach that the lysis reaction increases the amount of bacteria retained by the filter and thereby removed from the blood; while a Zierdt (US Patent 4,435,505) teach safe device to allow blood analysis without contamination. No more than routine skill would have been necessary to include an enclosed device, a lysis reagent and step in the method of detection, since the art teaches that it is desirable to rid a blood sample of substantially all blood cells since it is difficult to conduct an analysis of the blood components without interference from external sources and red blood cells when testing for microbial contamination. Moreover, there would have been a reasonable expectation of success in this modification since the art teaches that the lysis reagent and step does not harm the contaminants yet prepares the blood sample for microbial detection and analysis without time consuming and expensive techniques.

Additionally, *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007), discloses combining prior art elements according to known methods to yield predictable

results, thus the combination is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It would have been obvious to incorporate the enclosed device of Zierdt (US Patent 4,435,505) and the lysis and second filter of Zierdt et al., (J. of Clinical Microbio.) into the method of detection as taught by Doshi et al., because the lysing solution is known to release intracellular bacteria and filtration is advantageous because it separates out bacterial pathogens without allowing further contamination from external sources; thus yielding predictable results to one of ordinary skill in the art at the time of the invention. Moreover, the combination would have yielded a reasonable expectation of success along with predictable results to one of ordinary skill in the art at the time of the invention. Thus, it would have been obvious to a person of ordinary skill in the art to combine prior art elements according to known methods that is ready for improvement to yield predictable results. The claimed invention is prima facie obvious in view of the teachings of the prior art, absent any convincing evidence to the contrary.

Claim Rejections - 35 USC § 103

6. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doshi et al., (US Patent 5,766,552 published June 16, 1998), Zierdt (US Patent 4,435,505 published March 6, 1984) and Zierdt et al., (J. of Clinical Microbio. 1982. Vol.

15(1):74-77) as applied to claims 1-5, 8, 10, 14-17, 23-27 and 37-40 above, and further in view of Cathey et al., (US Patent 5,798,215 published August 25, 1998).

The claims are drawn to a method for detecting contaminating microbes comprising a marker agent that comprises a fluorescent marker or an agent coupled to a flurochrome or an enzyme enabling degradation of substrate thereby made fluorescent wherein the fluorescence is produced using an excitation laser and detected.

The teachings of Doshi et al., Zierdt (US Patent 4,435,505) and Zierdt et al., (J. of Clinical Microbio.) have been discussed above. However none teach a fluorescent marker or an agent coupled to a flurochrome or an enzyme enabling degradation of substrate thereby made fluorescent wherein the fluorescence is detected by an excitation laser wherein the method is performed in an enclosed and sterile device.

Cathey et al., teach analyte detection assays wherein the assay platform comprises a filter (col. 6, lines 19-21). The separation means for separating sample components may be positioned in the flow path of the assay platform (col.6, lines 54-56). For example, a filter may be positioned such that in when samples comprise red blood cells, the red blood cells are retained while serum flows through the filter (col. 6, lines 56-60). Depending upon the nature of the sample, the sample may be subjected to prior treatment, such as filtration or cell separation (col. 12, lines 15-19). Cathey et al., teach for blood, one of skill in the art can remove red blood cells to provide plasma or serum (col. 12, lines 20-21). Upon substrate addition, the substrate flows into the main flow path, where it is converted by an enzyme to a detectable product (col. 14, lines 34-

36). Cathey et al., the method being performed in an enclosed and sterile housing comprised within the device (Figures 1,2 and 4). Fluorescent labels or enzymes are preferred because they convert substrates to non-diffusible dyes that are used in signal producing systems (col. 13, lines 60-64). These signal systems also provide for wider testing capabilities and are useful in microbial detection/diagnosis (col. 13, lines 64-66). Cathey et al., teach optical signals are detectable and relate to the presence and/or amount of analyte in the sample include emissions, e.g. from fluorescent labels or the fluorescence of a quenching member of a signal producing system (col. 14, lines 53-56). The optical signals are detected by a wide variety of means including devices that measure absorbance, transmissions, diffraction, resonance which includes lasers (col. 15, lines 13-34).

Therefore, it would have been *prima facie* obvious at the time of applicants' invention to modify the method of Doshi et al., Zierdt (US Patent 4,435,505) and Zierdt et al., (J. of Clinical Microbio.) to include a marker agent that comprises a fluorescent marker or an enzyme enabling degradation of substrate thereby made fluorescent wherein the fluorescence is detected by an excitation laser as taught by Cathey et al. because Cathey et al., teach that fluorescent labels convert substrates to non-diffusible dyes are used in signal producing systems. No more than routine skill would have been necessary to include an enclosed device, a lysis reagent and step in the method of detection, since the art teaches that it is desirable to rid a blood sample of substantially all blood cells since it is difficult to conduct an analysis of the blood components without interference from external sources and red blood cells when testing for microbial

contamination. Moreover, there would have been a reasonable expectation of success in this modification since the art teaches that the lysis reagent and step does not harm the contaminants yet prepares the blood sample for microbial detection and analysis without time consuming and expensive techniques.

Additionally, *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007), discloses combining prior art elements according to known methods to yield predictable results, thus the combination is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". There would have been a reasonable expectation of success in this modification since only routine skill would have been required to use fluorescent agents coupled with an enzyme substrate when Doshi et al., already teach microbial detection with enzymatic substrates; thus yielding predictable results to one of ordinary skill in the art at the time of the invention. Moreover, the combination would have yielded a reasonable expectation of success along with predictable results to one of ordinary skill in the art at the time of the invention. Thus, it would have been obvious to a person of ordinary skill in the art to combine prior art elements according to known methods that is ready for improvement to yield predictable results. The claimed invention is prima facie obvious in view of the teachings of the prior art, absent any convincing evidence to the contrary.

Claim Rejections - 35 USC § 103

7. Claims 9 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doshi et al., (US Patent 5,766,552 published June 16, 1998), Zierdt (US Patent 4,435,505) and Zierdt et al., (J. of Clinical Microbio.) as applied to claims 1-5, 8, 10, 14-17, 23-27 and 37-40 above, and further in view of further in view of Besson-Faure et al. (US Patent 6,168,925).

The claims are drawn to a method for detecting contaminating microbes comprising a specific antibody to a platelet antigen such as anti-GpIIb/IIIa.

Doshi et al., Zierdt (US Patent 4,435,505) and Zierdt et al., (J. of Clinical Microbio.) have been discussed above however none teach a specific antibody to a platelet antigen such as anti-GpIIb/IIIa.

Besson-Faure et al., teach the anti-GpIIb/IIIa antibody as a specific antibody to a platelet antigen that causes aggregation. Besson-Faure et al., teach the analysis of platelet GpIIb/IIIa receptors (col. 1, lines 5-8). Activated platelets have this receptor which binds with very high affinity and causes aggregation of the platelets with each other (col. 1, lines 25-30). The activation of the platelets allows the receptor to bind with high affinity, which causes aggregation (col. 1, lines 27-31). The molecules also remain in circulation for long periods of time (col. 1, lines 57-60). Besson-Faure et al., teach anti-GpIIb/IIIa antibodies are publicly available (col. 3, lines 1-10).

Therefore, it would have been *prima facie* obvious at the time of applicants' invention to modify the method of Doshi et al., Zierdt (US Patent 4,435,505) and Zierdt et al., (J. of Clinical Microbio.) to include the anti-GpIIb/IIIa antibody as a specific

antibody to a platelet antigen as taught by Besson-Faure et al., because Besson-Faure et al., teach the a superior aggregation properties of anti-GpIIb/IIIa. No more than routine skill would have been necessary to include anti-GpIIb/IIIa in the method of detection, since the prior art teach that it is desirable to use antibody agglutinating agents that are quick, efficient at cluster formation, and fast acting and Besson-Faure et al., teach the anti-GpIIb/IIIa agglutinating agent which efficiently causes high affinity agglutination.

Additionally, *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007), discloses combining prior art elements according to known methods to yield predictable results, thus the combination is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It would have been well known and there would have been a reasonable expectation of success in this modification since only routine skill would have been required to use antibodies as agglutinating agents when the prior art provides motivation for antibody agglutinating agents wherein the motivation is that antibodies are reactive, well known for agglutinating properties and recognize glycoproteins; and Besson-Faure et al., provide commercially available anti-GpIIb/IIIa agglutinating antibodies that cause high affinity agglutination. Moreover, the combination would have yielded a reasonable expectation of success along with predictable results to one of ordinary skill in the art at the time of the invention. Thus, it would have been obvious to a person of ordinary skill in the art to combine prior art elements according to known methods that is ready for improvement

to yield predictable results. The claimed invention is prima facie obvious in view of the teachings of the prior art, absent any convincing evidence to the contrary.

Conclusion

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Primary Examiner, Art Unit 1645